Advancing Transfusion and
Cellular Therapies Worldwide

January 12, 2006

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852-1448

Docket No. 2005D-0330, 03 October 2005, "Draft Guidance for Industry and FDA Review Staff on Collection of Platelets by Automated Methods"

Dear Docket Manager:

AABB is an international association dedicated to advancing transfusion and cellular therapies worldwide. Our members include more than 1,800 hospital and community blood centers and transfusion and transplantation services as well as approximately 8,000 individuals involved in activities related to transfusion, cellular therapies and transplantation medicine. For over 50 years, AABB has established voluntary standards for, and accredited institutions involved in, these activities. AABB is focused on improving health through the advancement of science and the practice of transfusion medicine and related biological therapies, and developing and delivering programs and services to optimize patient and donor care and safety.

AABB formed a work group to study and critique the recommendations listed in the draft *Guidance for Industry and FDA Review Staff on Collection of Platelets by Automated Methods* and has identified several areas that we believe 1) require clarification, 2) would be improved through use of alternative language, or 3) should be removed from the document.

Following the General Comments listed below, each specific item we address in this correspondence is formatted as follows:

Text – language from the draft guidance (along with page # and other identifying information) is reprinted;
Recommendation – action that AABB recommends should be taken; and
Comments – rationale for the AABB recommendation.

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General Comments

1. Many of the regulations found in Title 21 of the Code of Federal Regulations (CFR) related to platelets are outdated. The language contained in this current draft guidance appears to be an attempt to work around the outdated regulations. One example is that of keeping a reference to pH at 6.0 because it is still in the CFR, yet at the same time adding recommendations for evaluating pH at 6.2 with action to occur at levels ≤ 6.2. We understand that the timeframe for revising regulations can be quite extended, and we appreciate issuance of this draft guidance. Nevertheless, we recommend that these regulations be updated.

2. Many of the recommendations will have a negative impact on the ability of facilities to provide an adequate inventory of platelet components, with no corresponding enhancements to donor or patient safety. One example of this is the restriction of plateletpheresis donations to 24 components per year rather than 24 collections (with multiple components) per year. A second example is the recommendation that a medical doctor be "present on the premises" when a plateletpheresis process is occurring. More detailed comments on these issues are provided in subsequent sections of these comments.

3. The references provided in the draft guidance for several proposed requirements did not provide data to support FDA's recommendations. Furthermore, other more pertinent references were omitted. Reference 10 (Patrono C, Coller B, Dalen JE, et al. Platelet-Active drugs. The relationships among dose, effectiveness, and side effects. Chest 2001 supplement; 119 (1): 39-63S) is a review article of issues pertaining to patients taking medications affecting platelet function. The conclusions that are drawn for such patient populations cannot and should not be extrapolated to the situation where platelets from a donor taking such medications are transfused into the circulation of a recipient not medicated with the same agents. An article specific to the function of transfused platelets (Stuart MJ et al, Platelet Function in Recipients of Platelets from Donors Ingesting Aspirin. NEJM 1972; 287:1105) is a more appropriate scientific study addressing the policy issue in the guidance document.

The Armed Services Blood Program Office (ASBPO) medication list is an example of utilizing a reference that has not been scientifically reviewed and is not evidence-based. FDA has stated publicly that this reference has been cited because it makes use of information from the Physician's Desk Reference (PDR). AABB believes this is an inappropriate use of the PDR. The PDR recommends the time persons should refrain from taking medication before surgery. However, this time is not directly applicable to the deferral period for plateletpheresis donation. It is not scientifically appropriate to equate donation eligibility issues to post-operative bleeding issues.

4. One of the major pillars of compliance is adherence to manufacturers' specifications. The contents of these specifications are rigorously reviewed by the FDA, and FDA approval of such documents essentially confers near-regulation status upon them. However, in many of the proposals in this draft guidance existing manufacturers'

instructions appear not be acknowledged, and in some cases, contradicted by the guidance. If this is the FDA's goal, it radically alters the FDA's long-standing recognition of use of manufacturers' specifications as a means of achieving regulatory compliance. We do not believe this is the FDA's intent. Thus, many of the AABB recommendations for changes emphasize the need for consistency with the FDA's long-held practice of basing regulatory compliance on adherence to manufacturers' instructions.

5. The AABB work group is aware that in response to this guidance document, many institutions have performed extensive data analysis on their plateletpheresis donors and their plateletpheresis programs and have submitted these data as part of their response to the docket. The work group has had the opportunity to briefly review some of these data and has concluded that since the methodologies across institutions are variable and the data are complex, a simple summary presentation of all these data in this document is not possible. In addition, the AABB work group is aware that some data analyses are still in the process of being completed. For these reasons, AABB strongly recommends that the FDA convene a workshop where both submitted data and data that are currently being collected can be presented, discussed, and evaluated in an open public forum. This workshop should be held prior to reissuing a revised draft guidance. AABB would be pleased to collaborate in development of such a workshop.

Comments to specific items begin with the following:

II. DISCUSSION

B. Definitions (p. 3)

Recommendation – Facility and Establishment are terms that should be included in the glossary of terms in this guidance.

Comment – The term establishment is not clearly defined but is used at various places throughout the document, leaving it open to multiple interpretations. The same comment applies to the term facility. Is facility the same as an establishment, or is facility intended to denote a fixed site? If these terms have been clearly defined in other FDA documents, then those documents should be referenced, and the terms should also be included in the glossary of terms in this guidance.

III. DONOR SELECTION AND MANAGEMENT

A. Donor Selection

Text: (p. 5, bullets 2 and 3)

- Prior to the first donation, test Platelets, Pheresis donors for levels of the following laboratory values that are acceptable under the manufacturer's directions for use:

- WBC Count
- Platelet Count

- If you cannot test the donor before the first donation (for example, because the donor presents at a mobile collection site), you should evaluate the donor's WBC and platelet counts after the first collection.

Recommendation – Delete this recommendation.

Comment – The value of determining the pre-donation platelet count is not unique to first time donors but also applies to repeat apheresis donors. Typically it is not a pre-count that is obtained, but a pre-collection sample that is drawn. A separate requirement for pre-donation platelet count in first time donors is not needed to enhance donor safety.

With regard to pre-donation WBC count, we are unaware of any manufacturer's directions for use of the WBC count. Furthermore, no rationale is stated in the draft guidance for why the WBC count should be obtained and evaluated.

Text: (p. 5, paragraph 2 and bullets 1 and 2 immediately following)
You should not collect Platelets, Pheresis from donors who have ingested drugs that adversely affect platelet function. These include, but may not be limited to:

- Aspirin (ASA)/ASA-containing drugs – 5 days from the last dose (Ref. 10)
- Non-steroidal Anti-inflammatory Drugs (NSAIDS) – 3 days from last dose (Ref. 9)

Recommendation – The requirement for lapsed time from last dose of Aspirin should be 36 hours.

Comment – There are two articles that specifically address the issue of aspirin ingestion by platelet donors and the length of time that platelet function is affected. The 36 hour deferral currently in the AABB *Standards for Blood Banks and Transfusion Services* (Reference Standard 5.4.1A) is supported by data presented in Stuart MJ et al: Platelet Function in Recipients of Platelets from Donors Ingesting Aspirin. NEJM 1972; 287:1105. This study compared bleeding time corrections in patients transfused with platelets from donors who had taken aspirin 36 hours prior to donation to results when patients were transfused with platelets from donors who had taken no aspirin. Correction was the same with the controls (no aspirin ingested by the donors) as with the platelets from donors who had ingested aspirin 36 hours prior to donating. An additional study by Slichter and Harker (Brit J Haematol 1976; 34:403) showed that in donors ingesting aspirin, the aspirin-induced platelet dysfunction was reversible in vivo in the transfusion recipients (leading to an appropriate correction of the recipient's bleeding time) within 6 to 18 hours.

The draft guidance does not provide data to substantiate the recommendation of five days as a necessary deferral period after aspirin ingestion. Reference 10, published in the

journal Chest, which looks at cardiac patients rather than a healthy "blood donor" population, states that 5 days is needed for 50% of platelets to be unaffected. However, a review of primary studies referenced in the Chest publication shows that only 10–30% of platelets need to be unaffected for total platelet function to be normal. Once aspirin is discontinued, new platelets produced by the marrow – about 10% of the population per day – are unaffected (Reference: O'Brien JR: Effects of salicylates on human platelets, Lancet 1968; 1:779). This manuscript and other articles, which show that platelet function returns to normal in 2-5 days after aspirin ingestion, are intended to assess risk in patients about to undergo surgical procedures, which is a different issue than aspirin ingestion in a platelet donor. These articles are therefore not pertinent in setting donor deferral guidelines.

Recommendation – Delete the recommendation pertaining to a deferral time subsequent to Non-steroidal Anti-inflammatory Drugs (NSAIDS).

Comment – NSAIDS affect platelet function through a mechanism that is reversible (NA Goldenberg, L Jacobsen, MJ Manco-Johnson. Brief communication: Duration of Platelet Dysfunction after a 7 Day Course of Ibuprofen PFA100. Ann Internal Med. 2005; 142: 506-509). Consequently platelets from a donor on an NSAID would be expected to function normally upon transfusion to a recipient not on a similar medication and there is no need for a donor deferral. In addition, the recommended 3 day donor deferral is not warranted in that the in vivo half-lives for most NSAIDS are less than 24 hours (Facts and Comparisons, January 2000, Drug Facts and Comparisons, p. 836-7).

Text: (p. 5)
Reference 9 cites the ASBPO Donor Deferral Criteria. Drugs and Medication Impact on Blood Donor Eligibility.
www.tricare.osd.mil/asbpo/library/policies/downloads/medication_list.doc

Recommendation – Delete the ASBPO medication list as a reference.

Comment – AABB does not believe that the Armed Services Blood Program Office medications list is an appropriate scientific reference. FDA should reference peer-reviewed published articles or recognized industry standards such as AABB *Standards for Blood Banks and Transfusion Services.*

We consulted with colleagues who helped develop the ASBPO list. They too expressed concern that it was being used for regulatory purposes as that was never the intent of the list. The ASBPO medication list has never undergone a rigorous scientific review, is not evidence-based, and was not intended for civilian use. The decisions for deferral were developed for unique situations faced by the Department of Defense. All blood collection organizations have medication lists. The list and recommendations found in the ASBPO list should not be assumed to be better than any other lists.

B. Donor Management

1. Platelet Count

Text: (p. 5, bullet 1)

- You should perform a pre-donation platelet count (Ref. 10), which will allow the device operator to more accurately set the target platelet yield parameters for each collection of Platelets, Pheresis. This is consistent with the device manufacturer's directions for use.

Recommendation – The Task Force recommends the following alternative language: "You should follow the device manufacturer's directions to set the target platelet yield parameters for each collection of Platelets, Pheresis."

Comment – A pre-donation platelet count is only one of the ways recommended by the manufacturer and approved by FDA to set the target yield parameters. Other options include:

- Average of the last three venous platelet counts;
- Utilize the platelet count obtained from a pre-collection venous blood sample of the donor's previous donations;
- Utilize average donor pre-platelet count for local donor populations; and
- Use the default count for the collection equipment being used.

(We note that Reference 10 may be a misprint since it is inappropriate reference for this recommendation.)

2. Donation Frequency

Text: (p. 6, bullet 1 and 2)
To protect the safety of the donor:

- A donor should undergo no more than 24 Platelet, Pheresis collections in a 12-month period.
- You should collect no more than 24 total Platelets, Pheresis components in a 12-month period. Two components collected from a double collection of Platelets, Pheresis and three components collected from a triple collection of Platelets, Pheresis would be counted as two components and three components respectively.

Recommendation – Delete the second bullet, concerning no more than 24 total components in a 12-month period.

Comment – Existing safety mechanisms already in place make this proposed guidance unnecessary. Imposing criteria in addition to a minimum platelet count of 150,000/uL and 500/600 ml plasma volume loss is not necessary to ensure donor safety and is unnecessarily restrictive.

It is our understanding that this recommendation is based on extrapolation from data provided in a single study examining the long term effects of repeated platelet donation (Lazarus EF, Browning J, Norman J, Oblitas J, Leitman SF. Sustained decreases in platelet count associated with multiple, regular plateletpheresis donations. Transfusion 2001; 41:756-61). This study assesses the difference in the initial and final pre-apheresis platelet count in 939 donors who donated on 11,464 occasions over a four year period. It should be noted that the study's conclusions are limited by the fact that the study was retrospective and draws on data from selective subgroups. Important parameters such as inter-donation, seasonal, and temporal variability and trends over time during the 4-year period are not analyzed. Despite showing some correlation between donor platelet count and donation frequency, the study did not show a relationship between the magnitude of platelet decrement and donation frequency at donation frequencies > 7.5 donations per year. Also there was no correlation shown between donor platelet count and the interval between donations or the number of platelets harvested. Consequently, this study does not provide any direct data to support the restriction of plateletpheresis donations to 24 components annually or to the lengthening of intervals to 7 and 14 days between donations for double or triple products. Indeed, the authors suggest that "clinically significant thrombocytopenia is unusual when rigorous ongoing review and prudent deferral policies are established and followed." Furthermore, the study findings have not been confirmed by independent investigators, despite the ready availability of data of this nature.

Secondly, this requirement will have an immediate negative impact on the ability to provide adequate inventories of platelets. This will jeopardize patient care, especially for those patients who are bleeding, undergoing chemotherapy, or are refractory to platelets. In many instances, facilities will find it impossible to maintain current levels of inventory. Today's extremely sophisticated platelet collection devices have allowed for many platelet donors to donate 24 times each year with the ability to provide a double product at each donation. A review of current data available to the work group is given below:

- In one center, if donations had been restricted to 24 components of Platelets Pheresis per year, there would have been a loss of 1,454 products, which equated to 13.7% of total platelet production. Recruiting additional apheresis donors to fill this void would require an increase in the donor base, estimated at 56-95% depending upon various assumptions involving how frequently newly recruited donors would donate and how many donors would be eligible to give double versus single products.
- Another facility reviewed their database to find that they had 230 of 2,836 donors donating >24 components, while not exceeding 24 collection sessions per year. Had donations been restricted to 24 components of Platelets Pheresis per year, there would have been a loss of 2,543 products, which equated to 10.6% of total platelet production.
- A loss of 3.5% would have been sustained by another facility that identified 45 donors who donated more than 24 platelet products in a 12-month period (303 out of 8,589 platelet components).

- A fourth center reviewed platelet collections in 2004 and determined that imposing a limit of 24 platelet products per year would have resulted in a loss of 946 products, amounting to approximately 6.2% of total apheresis platelet production.

Text: (p. 6, item 2, bullets 3-5)

- The interval between each collection of Platelets, Pheresis should be at least two (2) days with no more than two procedures in a 7-day period.
- The interval between collection of a double Platelets, Pheresis and any subsequent collection of Platelets, Pheresis should be at least 7 days.
- The interval between collection of a triple Platelets, Pheresis and any subsequent collection of Platelets, Pheresis should be at least 14 days.

Recommendation – Delete bullets 4 and 5 concerning intervals following double and triple collections.

Comment – We are not aware of any evidence to support a position that donor safety is compromised under current donation policy, nor do we see evidence to support changing current allowable ranges to the more restrictive ones listed for donation intervals following collection of a double or triple product. Adherence to a minimum platelet count of 150,000/uL and to device manufacturer's instructions to ensure that there is not excessive plasma loss will provide adequate safeguards for donor safety and will preclude donation at an excessive frequency.

Furthermore, from an operational standpoint it will be exceedingly difficult, if not impossible, to track these complicated donor eligibility algorithms using currently approved blood establishment computer software.

Text: (p. 6, item 2, bullet 6)

- A post-donation platelet count should be performed after each collection.

Recommendation – Delete this recommendation.

Comment – We do not believe a post-donation count is necessary to protect the health of the donor. During many collective years of experience performing plateletpheresis collections without routinely collecting post donation counts, no significant donor safety problems have been reported. Data compiled by Hemacare specifically for this submission show that in 105 donors undergoing standard plateletpheresis procedures with collections of single, double, or triple products, post-donation platelets never dropped below 100,000/μL, indicating that no donors were placed at risk. Furthermore, in all cases in which the post donation count fell below 150,00/μL, the pre-donation count prior to the next plateletpheresis (at two to four weeks following the index donation) had risen to well above 150,000/μL. See Appendix II.

In addition, there are technical difficulties in obtaining an accurate post-donation platelet count. Post-donation counts can be artifactually low due to difficulty in obtaining fully mixed or adequate samples, thereby giving a false impression of the donor's hematological status and risk of bleeding. Secondly, the collection of an adequate post-donation sample causes undue loss of additional donor red cells due to the need to rinse the lines of non-blood material and platelet depleted blood returning from the apheresis device.

For the purpose of eligibility for a subsequent plateletpheresis, a pre-donation platelet count provides a more accurate reflection of the donor's platelet status than does a post-donation count from the prior donation. (See Appendix II.) Nevertheless, we are aware that some facilities choose to use this post-donation count to evaluate the donor's eligibility for a future collection. Since this policy errs on the side of donor safety by potentially disqualifying otherwise acceptable donors from a subsequent apheresis, we believe that the option of obtaining a post-donation count should be retained, as is indicated in AABB *Standards for Blood Banks and Transfusion Services* (Standard 5.5.3.5.2).

4. Total volume loss per collection procedure

Text: (p. 7, item 4)
The total volume (excluding anticoagulant) of all blood components retained per collection of Platelets, Pheresis should not exceed 500 mL (600 mL for donors weighing 175 lbs or greater) or the volume described in the labeling for the device, whichever is less.

Recommendation – Revise to "The total volume (excluding anticoagulant) of all blood components retained per collection of Platelets, Pheresis should meet the device manufacturer's requirements as delineated in the device label."

Comment – FDA has already approved some devices that collect more than the proposed limits in this guidance. For example, per the Gambro Trima, 510(k) number BK990025, cleared April 7, 2000, the plateletpheresis collection can be up to fifteen percent (15%) of total blood volume (TBV). Medical Directors should be able to rely upon the cleared labeling of the devices to determine limits on collection volumes.

D. Medical Coverage

Text: (p. 7)
We believe that a physician should be present on the premises during the collection of Platelets, Pheresis to ensure that necessary medical treatment be available to the donor in a timely fashion. We interpret "present on the premises" to include a qualified physician able to arrive at the premises within 15 minutes (Ref 11). In case of an emergency, calling 911 may be used to obtain emergency medical care and transportation to another

facility for further care, but we do not believe this is a sufficient substitute for an available physician as previously described.

Recommendation – Revise to state that qualified medical care be available to the donor and define qualified medical care to include physicians and emergency response professionals.

Comment – Today, platelets are safely collected in a wide variety of settings that include mobile units and neighborhood collection centers. Experience shows that adverse reactions are rare in these donors and there is to no evidence to suggest that current protocols are inadequate to ensure donor safety. Current apheresis instruments have an extremely high rate of reliability, utilize low extracorporeal volumes and minimize citrate usage. Data from one facility concerning donor reactions is attached and reveals that adverse reactions in fact occur at a lower rate in plateletpheresis donors than in whole blood donors. (See Appendix I.) The task force notes that these data are representative of the number and type of donor reactions that occur nationwide in plateletpheresis donors. In addition, the work group reviewed data from donor fatality reports to the FDA through 2004 (obtained through FOIA) and notes that the data do not indicate any donor fatalities due to plateletpheresis donation. In fact, there is no evidence that fatalities in plateletpheresis centers are greater than that at whole blood collection facilities.

The AABB Hemapheresis Committee conducted a survey of the incidence of adverse effects of apheresis donation in a large series of donations at multiple centers (BC McLeod et al: Frequency of immediate adverse effects associated with apheresis donation. Transfusion 1998;38:938-943.). The study concluded "that apheresis donation is a safe undertaking, suitable for voluntary blood donors, with a very low risk of serious adverse effects. The risk of unconsciousness is lower than that found in many studies of whole-blood donation."

Taken together, multiple lines of evidence indicate that there is no need for a change in current levels of medical coverage.

We believe it is more appropriate to have a well-constructed viable plan to ensure timely access to medical care. Current Biologics License Applications requirements ensure that an applicant's plan for management of a cardiopulmonary emergency, including steps for contacting the physician, transport of the donor, etc., is reviewed by FDA during the submission review process.

Implementation of the draft guidance recommendation would have an immediate and dramatic effect on the ability to collect adequate platelet inventories. Most facilities have one medical doctor on staff. The draft guidance language would, in many instances, restrict a facility to one collection shift per day at one fixed collection site. We provide the following estimates of the impact of this recommendation at two large blood centers.

- At one center, enforcement of the proposed medical coverage guidelines would negatively impact plateletpheresis collections by 89%. Current collections would drop from about 15,500 to 1,700 per year.

- A second center estimated that collections would decrease by 93% assuming collections would need to be confined to the main collection center from Monday through Friday.

IV. INFORMATION PROVIDED TO THE DONOR (p. 7-8)

Comment – In general, this section of the guidance contains too much detailed information and should be simplified. In particular we have concerns with

Text: (p. 8, bullet 2)

- A statement that long-term effects of repeated plateletpheresis on the donor's platelet and leukocyte count is not understood.

Recommendation – Delete this recommendation or revise to "No long term adverse effects have been reported in frequent plateletpheresis donors."

Comment – Since no long term adverse effects have been reported, we do not believe it is necessary to include this statement with information provided to the donor. However, if a statement must be included, it is more accurate to indicate that there are no data to indicate any harmful effects. Discussions in the literature that address the possibility of long term adverse effects raise this as a speculative concern rather than a firm conclusion.

Text: (p. 8, bullet 3)

- A description of the number of Whole Blood, apheresis Red Blood Cells or plateletpheresis collection procedures and/or components that may be collected per year, and the donation interval for each.

Recommendation – Delete this recommendation.

Comment – As per our previous Comment we believe the recommended intervals between double and triple collections are not necessary. This requirement for a description of the rules about allowable intervals between collections for the various components would lead to an inordinately complex and lengthy description for donors. The number of variations that can be calculated for donation schedules is complex and requires tracking through use of computer tables. It would be nearly impossible to develop a document that contains all the scenarios. Any such document would be generic in nature and not informative to the individual donor.

V. COMPONENT COLLECTION AND MANAGEMENT

B. Target Platelet Yield

Text: (p. 8)
To assure that each component obtained from a multiple collection of Platelets, Pheresis results in an actual platelet yield of at least 3.0×10^{11} platelets, you should use the following targets. When collecting:

- Double components, the device's target platelet yield setting be at least 6.5×10^{11}.
- Triple components, the device's target platelet yield setting be at least 10.0×10^{11}.

Recommendation – Delete this recommendation.

Comment – FDA should encourage facilities to utilize validation and monitoring data and work with the respective manufacturer to determine the appropriate targets. Apheresis collection facilities experience different precision with respect to platelet yield predictions based on variation in laboratory methods, hematology analyzers, apheresis practices, and apheresis devices. It is inappropriate for the agency to set these targets as many locations successfully use alternative target yields. Furthermore, the proposed target yield numbers may not be accurate in the future as new instruments with improved technology are developed.

C. Hemolysis during collection

Text: (p. 8 – 9)
During the course of the apheresis collection procedure, you should visually inspect the separated plasma for hemolysis. A red tinge to the plasma in the return line is cause for evaluation (prior to re-infusion to the donor) to determine whether this is a result of red blood cell contamination of plasma or from hemolysis.

Recommendation – Revise to "Follow the manufacturer's directions for monitoring and responding to possible hemolysis should it occur during the collection procedure."

Comment – We believe it is appropriate to defer to manufacturer's directions, as there are instances in which the draft guidance language is not applicable. For example, visual inspection would not be helpful using today's continuous flow apheresis instruments, especially in single needle procedures where there is constant switching by the instrument between draw from and return to the donor.

VI. PROCESS VALIDATION

Comment – The AABB work group found it very difficult to understand how this section on Process Validation should be implemented. Even those members whose primary

responsibilities are for Quality Assurance and submission of BLAs were unable to clearly decipher the intent and meaning of some of the proposed requirements, as well as the expectation for implementation. The following specific comments are based on our best interpretation of this section of the draft guidance.

Text: (p. 9, paragraph 3, bullets 1-5)
In addition, you should perform Process Validation on the following devices used in the collection process:

- Blood cell counting devices, including devices used to determine the residual WBC count in leukocyte reduced components.
- pH measurement:
  We recommend that a pH meter be routinely used rather than pH (nitrazine) paper.
- The scale used to weigh the components
- Sterile tubing welders used to attach leukoreduction filters or sampling containers (Ref. 13)
- Shipping containers

Recommendation – Revise the language to focus on the entire process rather than the specific devices. "In addition, you should perform Process Validation on the following processes used in the preparation, shipping and measurement of Platelets Pheresis:

- Blood cell counting: platelets and residual WBC;
- pH measurement: We recommend that a pH meter or blood gas analyzer be routinely used rather than pH (nitrazine) paper;
- Component weighing;
- Sterile connection methods; and
- Preparation of blood components for shipping: Shipping containers should be appropriate for this purpose."

Comment – The listed devices are not used in the collection process. Rather, these are devices that may be used in various steps in the process: such as preparation, shipping, and measurement of Platelets Pheresis.

B. Validation Protocol

Text: (p. 10, bullet 2, sub-bullet 2)

- Minimum/maximum acceptable values for the Platelets, Pheresis collection and or component as specified by the device manufacturer (see 21 CFR 606.60(a)).
  - Target platelet yield

Recommendation – Delete Target platelet yield from this list.

Comment – It is our understanding that a target platelet yield is a fixed value, and is donor dependent. Although it serves as the collection target, it is not an actual measured value. For this reason, we do not understand how a minimum or maximum target platelet yield value would be defined and integrated into a validation protocol, nor do we understand why this would be necessary.

D. Product Performance Qualification (Component Collection)

Text: (p. 11, paragraph 1)
Qualification should include testing for the actual platelet yield, pH, volume, residual WBC count and percent component recovery (for leukoreduced components, RBC/hematocrit (if applicable) and bacterial contamination testing (Table 1).

Recommendation – Revise to "Qualification should include testing for the actual platelet yield, pH, volume, residual WBC count and percent component recovery (for leukoreduced components, if applicable), and RBC/hematocrit (if applicable)."

Comment – Percent component recovery only applies to leukocyte reduction by filtration that occurs after collection, and does not apply to leukocyte reduction by process. See below for comments regarding bacterial contamination testing.

Text: (p. 11, paragraph 2, bullet 1)

- Test a minimum of 60 consecutive single (30 for double and 20 for triple) collections for each type of automated blood cell separator for (1) actual platelet yield, pH, volume, visible RBCs; and (2) for residual WBC count and percent recovery (Ref.2), with 0 failures in each category. Another option is to test 93 consecutive single (47 for double and 31 for triple), which allows for 1 failure…

Recommendation – Delete visible RBCs from this list.

Comment – Appropriate actions for handling Platelets Pheresis with visible RBCs in platelets are incorporated into routine standard operating procedures, and need not be included in a validation protocol. AABB *Standards for Blood Banks and Transfusion Services* (Standard 5.14.5) requires a crossmatch if the platelets are not ABO compatible or not produced from a method known to result in < 2 mL of red blood cells. Contamination with >2mL of RBC in Platelets Pheresis is grossly obvious to the naked eye and occurs only in special circumstances.

Text: (p. 11, paragraph 2, bullet 1 continued)
…Perform bacterial contamination testing on 500 collections with 0 failures…

Recommendation – Delete this statement from the bullet.

Comment – Bacterial contamination testing is a quality control test, not a product qualification requirement. Validation of the bacterial contamination testing methodology selected for use within a facility occurs prior to the methodology being implemented for routine use. In addition, current industry standard is to perform bacterial testing on 100% of products. Therefore, the inclusion of bacterial testing in process validation is not necessary.

Text: (p. 11, paragraph 2, bullet 1, continued)

- For facilities using automated blood cell separators from a single manufacturer only, we recommend that:
  - All devices be included in the initial product performance qualification; and
  - Additional devices of the same model be included in monthly QC testing only.

- Product performance qualification should be completed for each automated blood cell separator used in your establishment.

Recommendation – Revise to "Product performance qualification should be completed for each automated blood cell separator (defined as manufacturer and model) used in your establishment. All devices should be included in the initial product performance qualification; and devices added after the initial qualification of the same manufacturer and model should be included in monthly QC testing only."

Comment – This language would clearly define manufacturer and model as the criteria to be applied to determine which automated blood cell separator would require product performance qualification. It is also not clear why this point would be applied only to facilities using devices from a single manufacturer. There are situations where a facility may be using devices from a single manufacturer, but there may be multiple model numbers in use.

The term establishment is not clearly defined, leaving it open to multiple interpretations. The same comment applies to the term facility. Is facility the same as an establishment, or is facility intended to denote a fixed site? If these terms are clearly defined in other FDA documents, then those documents could be referenced, and the terms should be included in the glossary of terms in this guidance. In the context of process validation, we believe that this activity need not be performed at each fixed site provided that all sites operate under the same standard operating procedures, training programs, etc.

Text: (p. 11, paragraph2, bullet 3)

- Qualification include Platelets, Pheresis collection by all trained personnel;

Recommendation – Delete this recommendation.

Comment – It is not necessary to include data on products from every person that is trained in the process.

Text: (p. 11, paragraph 2, bullet 4)

- Residual WBC count be performed within 24 hours of collection, or per manufacturer's directions for the cell counting methodology (Ref 2);

Recommendation – Revise language to read "Samples should be handled, prepared, and processed without delay according to the requirements of the WBC counting method to ensure that a true and representative count is obtained."

Comment – Our recommended language is identical to the language in Ref 2 (FDA Recommendations and Licensure Requirements for Leukocyte-Reduced Blood Product, May 29, 1996). If a timeframe for a counting method has been internally validated, that timeframe should be acceptable. It is not clear why 24 hours is mentioned in this draft guidance. AABB has reviewed manufacturer's directions and notes that some of them allow for counting to occur at times that exceed 24 hours. For example, FACSCaliber and BD Leucocount allow for WBC counting to be completed within 48 hours of the product being leukoreduced.

Text: (p. 11, paragraph 2, bullet 5)

- An RBC count/hematocrit be performed on Platelets, Pheresis or concurrent Plasma (when collected) containing visibly apparent RBCs to determine total packed RBC volume. You should hold Platelets, Pheresis containing more than 2 mL of RBCs until the residual WBC count has been determined and found to be less than 5.0×10^6 for platelet or plasma components labeled as leukocyte reduced;

Recommendation – Delete this recommendation.

Comment – This information is incorrectly placed in the guidance. The specific action for Platelets Pheresis with visibly apparent RBCs is very important and should be included in an operational SOP but should not be included in a qualification plan. Operationally, it will be important that the SOP specifies actions to be taken for each product with visibly apparent RBCs.

Text: (p. 12, bullet 1)

- Perform bacterial contamination testing using a CBER cleared or approved bacterial detection system specifically labeled for testing of plateletpheresis components (Refs. 16, 17, 18, and 19), used in the manner for which it was cleared or approved.

Recommendation – Delete this recommendation from Product Performance Qualification.

Comment – Bacterial contamination testing is a quality control test, not a product qualification requirement. Validation of the bacterial contamination testing methodology selected for use within a facility occurs prior to the methodology being implemented for routine use. In addition, current industry standard is to perform bacterial testing on 100% of products. Therefore, the inclusion of bacterial testing in process validation is not necessary.

Text: (p. 12, bullet 2)

- Conduct an investigation of component qualification failure, and when appropriate, initiate corrective action and follow-up measures. We understand that some failures may occur due to conditions **not** resulting from a failure of the process. Examples of non-process failures include positive bacterial contamination testing resulting from the collection from a donor with asymptomatic bacteremia.

Recommendation – Additional examples to illustrate non-process failure or further explanation of non-process failures would be helpful.

Table 1 Collection Performance Qualification Criteria

Recommendation – We propose that Table 1, with footnotes, be revised as follows:

Test	Unit of Evaluation	Performance Criteria	Target	Acceptance Criteria[1,2] (#units evaluated / #failure)	
Actual Platelet yield	**Per transfusable product**	**$> 3 \times 10^{11}$ platelets meet manufacturer's requirements**	**90/90**	**22/0**	**38/1**
Volume	**Per transfusable product**	**meet manufacturer's requirements**	**90/90**	**22/0**	**38/1**
Residual WBC content	**Per collection**	**$\leq 5 \times 10^{6}$**	**95/95**	**60/0**	**93/1**
% recovery following leukocyte-reduction[3]	**Per collection**	**≥ 85% component retention**	**95/95**	**60/0**	**93/1**
pH	**Per transfusable product**	**≥6.0 ≥6.2**	**90/90**	**2 months QC 22/0**	**2 months QC 38/1**

Footnotes

1. Samples should be stratified over single, double, and triple collection procedures as applicable. For example: 20 single collections, 20 double collections, and 20 triple collections. A facility or a method that would not include the collection of triples might perform 30 single and 30 double collections for initial qualification. Total sample size and acceptance criteria should be selected prior to initiation of validation (e.g., 60 collection with zero failure or 93 collections with one allowable failure). This approach is based on dichotomous outcomes (pass or fail). Other approaches using continuous outcomes and statistical approaches resulting in fewer required collections may be applied.

2. Process failures only; non-process failures should be excluded.

3. This outcome is applicable only to WBC reduction processes using secondary methods such as filtration, i.e. when leukoreduction is performed secondary to the collection process. This does not apply when leukocyte-reduction is performed automatically as part of the automated process.

Comments – Table Organization and Column Titles

- Column 2 titled "Unit of Evaluation" was added to define the unit to be evaluated – i.e. whether the requirement pertains to a transfusable product or to an entire collection.

- Column 3 titled "Acceptance Criteria" was changed to "Performance Criteria" in order to use Acceptance Criteria as a title for the final column.

- Column 5 titled "Allowable Process Failure" was changed to "Acceptance Criteria" and # units evaluated / # failures was included as criteria in these final columns to determine whether the process is acceptable.

- The row titled "pH" was moved to the bottom of the table as this involves routine QC that will be submitted with the validation data.

- Row 3 titled "Residual WBC count; component recovery" was split into two rows as there are two outcomes to be determined.

- Row 5 titled "Red blood cell count" was deleted because we deleted the requirement from the qualification testing criteria.

- The row titled "Bacterial Contamination Testing" was deleted for reasons provided above.

Comments – Content of Table

Comment – Acceptance Criteria
We recommend that several performance criteria be changed to 90% at 90% confidence rather than the 95%/95% proposed in this guidance document. Using the same statistical formulation as in the current guidance document, our proposal results in a change in the acceptance criteria to 0 failures out of 22 procedures or 1 failure out of 38 procedures.

Comment – Actual Platelet Yield
The target criteria for a transfusable platelet product should be 90 % $\geq 3.0 \times 10^{11}$ at 90% confidence. The target level of 90% of products with a yield above the specified lower limit is consistent with AABB *Standards for Blood Banks and Transfusion Services* (Standard 5.7.5.19); the additional requirement for 90% confidence applies additional stringency to the AABB Standard. The requirement of "95% confidence that 95% of components" will pass is too stringent due to two factors: 1) biological variability of the donor that may cause actual platelet yields to vary from donor to donor despite similar target yields and 2) automated hematology analyzers currently used to obtain platelet counts on platelet rich plasma are imprecise. Failures may be due to counting issues, not product failures (Moroff et al: *Transfusion Medicine Reviews,* Vol 19, No 2 (April), 2005:pp 155-165).

Comment – Volume
There should be no volume specification for divided products (double/triple) beyond the manufacturer's criteria for storage containers and minimum transfusable unit for platelets of 3×10^{11} platelets. As with platelet yield, we propose that the target criteria should be 90% compliance with 90% confidence, reflecting the industry approach to platelet yield in AABB Standards.

Comment – Residual WBC Content
Deleted requirement for residual WBC count "per component for double and triple collections." If the collection meets this requirement, then each component (split) will also meet this requirement.

Comment – % Recovery Following Leukocyte Reduction
This identifies that the outcome is only applicable to Platelets Pheresis leukoreduced by secondary methods, such as filtration. See proposed revision to Table 1, footnote 3.

Comment – pH
The target pH should be 90% $\geq$ 6.2 with a confidence level of 90%. As reported in the draft Guidance Reference 6, actual experience indicates that at outdate, 1 pH failure might be expected in 24 products. Therefore, 90% compliance with 90% confidence is the appropriate performance criteria to reflect acceptable performance (i.e. acceptance criteria of 0 failures in 22 or 1 failure in 38). This testing should be done as described in the last bullet on p. 11 – 1/3 in the first third of the dating period, 1/3 in the second third of the dating period, and 1/3 the day of outdate.

We propose that pH results be reported for two consecutive months in lieu of including these data in the product qualification. The manufacturers have already provided data as a basis of approval, demonstrating acceptable storage characteristics if the device is used according to the manufacturer's directions. We believe additional pH data from the local site are not needed, in advance, to show that the device performs according to the manufacturer's claims in the hands of the local facility. Accumulation of 2 months of operational data provides a better snapshot of the process and may prevent undue wastage of apheresis platelets which would be purposefully outdated for this testing.

VII. QUALITY ASSURANCE (QA) AND MONITORING

A. Standard Operating Procedures (SOPs) and Record Keeping

1. Requirements for SOPs

Text: (p. 14, bullet 1)

- Your written SOPs must include minimum and maximum values for a test or procedure when it is a factor in determining donor acceptability (21 CFR 606.100(b)(2)).

Recommendation – Revise to "If applicable, your written SOPs must include minimum and maximum values for a test or procedure when it is a factor in determining donor acceptability (21 CFR 606.100(b)(2))."

Comment – There are some tests or procedures for which only a minimum or maximum value may be needed to determine donor acceptability. For example, there should be no requirement for a lower limit for blood pressure. AABB *Standards for Blood Banks and Transfusion Services* have never required a lower limit for blood pressure, and it is not standard procedure for blood collection facilities. Current European requirements also do not specify a lower limit for blood pressure. The AABB Standards Committee revisited this issue in 2004 and once again decided against requiring a lower limit for donor blood pressure because there is not enough scientific data to support such a requirement.

2. Additional Provisions Applicable to SOPs

Text: (p. 14, bullet 5)

- **Bacterial Contamination testing:**
  - The instruction circular must state that, if the storage container is entered transfusion of the component must be initiated as soon as possible, and no more than 4 hours later (21 CFR 606.122(l)(2).

Recommendation – Revise to "Blood components have been prepared by techniques that aid in preserving sterility up to the time of expiration. If the container is entered in a manner that violates the integrity of the system, the component expires 4 hours after entry if maintained at room temperature (20-24 C), or 24 hours after entry if refrigerated (1-6 C)."

Comment – This is the language in the current *Circular of Information for the Use of Human Blood and Blood Components* (Circular).

Text: (p. 15, bullet 1)

- **Actual Platelet Yield**: The platelet yield from each collection of Platelets, Pheresis should be provided to the transfusion facility.

Recommendation – Delete this recommendation.

Comment – Routinely providing this information to the transfusion facility would create a burden of record keeping with no patient benefit. The majority of clinicians do not make therapeutic decisions based on the number of platelets contained in an apheresis unit. Since a platelet yield will have been determined for all plateletpheresis products, clinicians can be informed by hospital transfusion services that such information is available and can be easily obtained if requested by the transfusing physician.

Text: (p 15, bullet 2)

- **Residual WBC counts:** Your SOP should state the maximum acceptable WBC limits for each automated blood cell separator device in use.

Recommendation – Revise to "Your SOP should state the expected WBC limits as defined by the manufacturer's instructions, as well as the maximum acceptable WBC limits of 5×10^6 per unit of leukoreduced component."

Text: (p. 15, bullet 5)

- **Total volume loss:** Annual volume loss should not exceed 12 liters (12,000 mL) per year for donors weighing 110-175 lbs; 14.4 liters (14,400 mL) per year for donors weighing more than 175 lbs (Ref. 3).

Recommendation – Revise bullet title to read "Annual total plasma volume loss."

Comment – Draft guidance Reference 3, a 1995 revision of the Requirements for Infrequent Plasmapheresis Donors Memorandum, addresses plasma volume loss, not total volume loss.

Text: (p15, bullet 6)

- **Leukocyte reduction filters:** CBER clears filters used to reduce leukocytes in Platelets, Pheresis for the filtration of specific components. You should use in-line or in-process leukocyte reduction filters.

Recommendation – Delete this bullet.

Comment – This statement is not appropriate for this guidance document. We agree that filters should be used per the manufacturer's instructions for use, and as cleared by FDA, but believe this is not the appropriate guidance document to address this issue.

Text: (p. 16, bullet 2, sub-bullet 2)

- You must follow the automated blood cell separator manufacturer's directions for use (21 CFR 606.60(a), 606.65(e)) and have provisions for the disposition of Platelets, Pheresis that have actual platelet yield or volumes that are outside of the limits of the automated blood cell separator manufacturer's specifications. If sterile docking of an additional container(s) is necessary, use a container(s) designed to achieve and protect a sterile conduit. You should use containers from the same manufacturer.

Recommendation – Revise last two sentences to "If sterile docking of an additional container(s) is necessary, use a container(s) designed to achieve and protect a sterile

conduit. The additional container(s) should be compatible or equivalent as defined by manufacturer's instructions."

Comment – We understand that claims are given for a particular collection device that include the container, however it should be permissible to sterile dock compatible or equivalent containers. They do not need to be from the same manufacturer.

B. Donor Monitoring

1. Platelet counts

Text: (p. 17, paragraph 1)
You should notify your Medical Director when a donor has a post collection platelet count less than 100,000/uL, and you should defer the donor until his/her platelet count has returned to at least 150,000/uL.

Recommendation – Delete this recommendation.

Comment – See prior comment (III. B. 2. Donation Frequency). To reiterate, we do not believe a post count on every donor is necessary. If a facility chooses to perform post counts, that facility should establish an alert level for notification of the Medical Director.

Text: (p. 17, paragraph 2)
Transient decreases in platelet counts have been reported in donors undergoing multiple collections of Platelets, Pheresis (Ref. 21). Although the effect of long-term regular collection of Platelets, Pheresis on donor platelet counts is unknown, clinically significant thrombocytopenia in these donors is unusual. You should review a donor's records before each donation to monitor the donor's ability to recover his/her baseline platelet count.

Recommendation – Revise to "Transient decreases in platelet counts have been reported in donors undergoing multiple collections of Platelets Pheresis (Ref. 21), however, clinically significant thrombocytopenia in these donors is unusual. You should review a donor's records before each donation to monitor the donor's eligibility for donation."

Comment – Current practice is to review each donor's records before donation to monitor the donor's eligibility for donation. This includes a review of donor platelet counts to assess the donor's ability to recover his/her platelet count. However, we disagree that the donor needs to return to his/her initial baseline platelet count (i.e., prior to their first plateletpheresis) to remain eligible as a donor.

The work group has had an opportunity to review data from frequent long-term platelet donors from several institutions. The initial analysis shows that the data are too complex to concisely summarize in a document of this type. An open public workshop would

provide the appropriate environment for discussion and review of the data and the methodologies used.

C. Component Testing

1. Daily component specification check

Text: (p. 18, bullet 1)

- Actual platelet yield after collection: Actual yields (volume x platelet count) must be determined at the conclusion of each appropriate phase of manufacturing (21 CFR 211.103), and should be determined prior to issue.

Recommendation – Revise to "Actual platelet yield after collection: Actual yields (volume x platelet count) should be calculated after collection and prior to the product being made available for distribution (i.e. after all sampling for testing has been completed)."

Comment – Platelet yield calculations are necessary at the conclusion of the collection process in order to ensure manufacturer storage specifications are met and again after QC sampling is complete in order to know the yield of the product that is made available for distribution. Intermediate calculations do not serve a purpose. An actual platelet count is necessary only at the first calculation. The final calculation would consist of the original platelet count x the volume remaining after all sampling is complete.

Text: (p. 18, last sub-bullet)

- Weight/volume conversion: A weight/volume conversion is necessary to determine the volume.

Recommendation – Revise to "When volume is determined gravimetrically (i.e., by weight), an appropriate weight to volume conversion factor (i.e., density) should be applied."

Comment – This statement may be overly restrictive for new technologies, which could possibly measure volume directly.

Text: (p. 19, bullet 1)

- Residual WBC count on all collections that do not utilize an automated leukocyte reduction methodology.

Recommendation – Delete this recommendation.

Comment – Universal leukocyte-reduction is not required either by statute, rule or industry standard in the United States. The various methodologies in use to achieve

leukoreduction of Platelets Pheresis have been reviewed and cleared for this application by FDA and should be treated as a standard process that has been appropriately qualified and subject to routine in-process controls. This is true for post collection process methodologies, such as filtration, as well as automated methodologies. There should not be a requirement to determine WBC content on 100% of these products.

Text: (p. 19, bullet 3)

- Bacterial contamination testing: as specified by the collection device manufacturer.

Recommendation – Revise to "Bacterial contamination testing should be conducted at the frequency and by the method established by the blood center after consideration of industry standards and any specific requirements by device manufacturers."

Comment – Collection device manufacturers do not uniformly or routinely require bacterial contamination testing. Bacterial testing is required by industry standard (AABB), and in some instances (e.g., 7-day platelet storage) is specified by the device manufacturer.

2. QC monitoring

Text: (p. 19, paragraph 2)
Under 21 CFR 211.160(b), laboratory controls must include the establishment of scientifically sound and appropriate specifications, standards, sampling plans and test procedures. One example of a scientifically sound statistical sampling plan is the use of scan statistics (see Appendix A). However, other statistical plans may also be appropriate. Statistical plans should:

- Use an alpha of 0.05 and a power of $\geq$ 80%.
- Detect a > 5% non-conformance rate.

Recommendation – Remove the reference to scan statistics and remove Appendix A.

Comment – We are in agreement that a sound statistical process should be incorporated into the Quality Assurance and Monitoring program. Further, we recognize and appreciate that CBER has devoted time and effort to developing the scan statistics approach, resulting in an intellectual contribution to the field (ref. Journal of Biopharmaceutical Statistics 2005:15;353-366.). However, we feel strongly that it is premature to add this to the guidance document. Although FDA has provided the option of using other statistical plans, the prominence given to scan statistics in the guidance document will likely lead to wide-scale adoption of this method. However, the use of scan statistics in process control is untested and its potential impacts on blood center operations are unknown. For example, we do not understand how the determination that 10% of products should undergo QC testing was derived in the scan statistics proposal and it is unclear how this requirement will impact blood centers.

We believe the agency should first partner in pilot studies with a cohort of blood establishments that reflects a range of manufacturing and operational practices. The major goal of these scan statistic pilot studies would be to determine if, when compared to currently used statistical approaches, scan statistics will improve the purity, potency and efficacy of plateletpheresis products. A secondary goal would be to determine the impact on quality assurance activities; it may be true that the scan statistics approach can be easily adopted in some operations, but it could be overwhelming in others.

We suggest that the issue of quality control monitoring needs more discussion and that this would be an important topic to include in a proposed workshop.

2. QC monitoring

Text: (p.19, paragraph 4, bullet 2)

- Include testing of components collected on each individual automated blood cell separator device.

Recommendation – Revise to "Include testing of components collected on each automated blood cell separator (defined as manufacturer and model) used by your establishment."

Comment – This language would clearly define manufacturer and model as the criteria to be applied when selecting a representative sample of products for QC monitoring.

Text: (p. 20, bullet 1)

- Test for percent component retention.

Recommendation – Revise to "Test for percent platelet recovery when product has been leukoreduced utilizing manual filtration methods."

Comment – This recommendation applies to products that are leukoreduced by a post collection manufacturing step. Component retention measures are not applicable to products that are leukoreduced by an automated leukocyte reduction methodology.

Text: (p. 20, bullet 2)

- Test for the residual WBC count (when applicable) within 24 hours after collection to reduce aberrant results due to cellular deterioration and clumping, or per the manufacturer's directions for the counting device or method used.

Recommendation – Revise language to read, "Samples should be handled, prepared, and processed without delay according to the requirements of the WBC counting method to ensure that a true and representative count is obtained."

Comment – Our recommended language is identical to the language in Ref 2 (FDA Recommendations and Licensure Requirements for Leukocyte-Reduced Blood Product, May 29, 1996). If a timeframe for a counting method has been internally validated, that timeframe should be acceptable. It is not clear why 24 hours is mentioned in this draft guidance. AABB has reviewed manufacturer's directions and notes that some of them allow for counting to occur at times that exceed 24 hours. For example, FACSCaliber and BD Leucocount allow for WBC counting to be completed within 48 hours of the product being leukoreduced.

Text: (p. 20, bullet 9)

- pH must be $\geq$ 6.0 (21 CFR 640.25(b)(2)) and should be $\geq$ 6.2 (Refs. 5 and 6).

Request for clarification – The recommendations for pH as outlined in this document are not at all clear. Please provide clarity for the recommendation for pH being evaluated at 6.0 and at 6.2. Include specific recommendations for the action(s) to be taken at each level.

Text: (p. 20, bullet 11)

- The volume in each container for double collections should be 50% $\pm$ 5%; for triple collections 33% $\pm$ 3%, or per the manufacturer's specifications.

Recommendation – Revise to "The volume for divided products should meet the manufacturer's criteria for containers designed to store a transfusable platelet product with a minimum platelet count of 3×10^{11} platelets."

Comment – There is no need to impose additional volume restrictions beyond those provided by the manufacturer.

Text: (p. 20, bullet 12)

- If one component from a double or triple collection procedure is found to have unacceptable results (less than 3.0×10^{11} platelets, pH <6.2, or a volume discrepancy), the corresponding component(s) from the collection should be quarantined until they are tested and found to be acceptable.

Recommendation – Revise to "Each facility should have written procedures, for each QC parameter to be measured, with defined courses of action to take when acceptance criteria are not met. The procedure should include consideration of the disposition of any co-components."

Comment – Procedures should be in place for all QC parameters that are measured. The recommendation as presented in the draft guidance, (particularly for platelet count and volume) are too restrictive. Generally, there would be no reason to quarantine the labeled products that have been made available for distribution.

F. Quality System Audits

Text: (p. 21, paragraph 3, bullet 3)

- Component bacterial contamination testing: Rates of bacterial contamination of plateletpheresis should be monitored, and rates that exceed 1:3000 (Ref. 7) should be considered potentially non-conforming, and an investigation be initiated.

Recommendation – Revise to "Component bacterial contamination testing: Rates of bacterial contamination of plateletpheresis should be monitored. The facility should set alert and action levels for positive rates based on their detection methods. There should be a plan established for investigation of rates exceeding expected levels."

Comment – Current methods employed in the United States vary. For example, baseline bacterial contamination rates have been determined using aerobic cultures only whereas some facilities perform both aerobic and anaerobic cultures. Since the baseline positive rates for these different testing schemes have not yet been determined, it is inappropriate for FDA to specify a specific rate at which action needs to be taken.

X. REPORTING CHANGES TO AN APPROVED BIOLOGICS LICENSE APPLICATION (BLA)

D. Component Submission for CBER QC Testing

Text: (p. 26 – 27)
To obtain a biologics license under Section 351 of the Public Health Service Act for any biological product, a sample(s) representative of the product must be provided with the application (21 CFR 601.2(a)). Samples of any lot of any licensed product may at any time be required to be sent to CBER (21 CFR 610.2(a)).

In compliance with these regulations:

- Licensed collection facilities with no prior experience in the collection of Platelets, Pheresis must schedule Platelets, Pheresis component submission for CBER QC testing. Licensed facilities that submit a CBE-30 for an additional facility under an approved Comparability Protocol do not need to send components for CBER QC testing.
- We may also request at any time that a facility submit components for CBER QC testing. In particular, we may require you to provide samples if, during our review of a submission, we determine that the submitted data is inadequate or if you are submitting an application under 21 CFR 640.120 to use procedures at variance with those required in regulation.

Recommendation – We believe the requirement for submission of platelet products should be removed.

Comment – We believe that the requirement to send platelet products to CBER for testing is an outdated practice that does not make a meaningful contribution to the safety and efficacy of the product or manufacturing process. Since this practice was initiated, the technology for collection and laboratory methods have made tremendous strides and progressed through several generations of development. At this point, we believe this activity unnecessarily consumes valuable blood products, as well as personnel and other resources at the blood centers and CBER. This requirement is not applied to red blood cell products or plasma products.

We suggest that FDA can obtain all necessary information related to the manufacturing process of Platelets Pheresis through examination of the qualification and QC records from the facility. We believe this approach will result in more timely turn around of license applications and sparing of resources both in the blood center and at FDA.

Thank you for the opportunity to provide comments to this draft guidance. AABB appreciates the time and effort that FDA has expended in preparing the draft guidance and we believe that our comments and suggested revisions will enhance the document. AABB would be pleased to collaborate in development of a workshop to address issues raised by the draft guidance.

Questions concerning these comments may be directed to M. Allene Carr-Greer, Deputy Director, Regulatory Affairs, AABB (acarrgreer@aabb.org).

M. Allene Carr-Greer, MT(ASCP)SBB
Deputy Director
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Appendix I

The following data are from one major blood collection center and compare Adverse Reactions from Platelets Pheresis Collections with Adverse Reactions from Whole Blood Donors from 1999 through 2005. These data indicate that adverse reactions occur at a lower rate in plateletpheresis donors than in whole blood donors

Platelets Pheresis Collections
Adverse Reactions

Year	Type I	Type II	Type III	Total Collections	Percent All Reactions
1999	6	3	0	1640	0.55
2000	11	7	1	4506	0.42
2001	9	4	0.	5006	0.26
2002	13	5	2	5310	0.38
2003	25	4	0	5842	0.50
2004	38	4	3	6541	0.69
2005	54	4	4	6572	0.94

Type I – pallor, perspiration, dizziness, sighing, nausea without vomiting, hyperventilation without other signs or symptoms

Type II – progression of all symptoms of a Type I reaction, bradycardia, shallow respirations, anxiety, vomiting

Type III – progression of all symptoms of a Type II reaction, hyperventilation with neuromuscular excitability, variable color (pale to cyanotic), incontinence, fainting, convulsive movements, true convulsions

Appendix I

Whole Blood Collections
Adverse Reactions

Year	Type I	Type II	Type III	Total Collections	Percent All Reactions
1999	235	23	25	24463	1.16
2000	682	61	86	82770	1.00
2001	1156	115	127	88813	1.57
2002	1422	50	130	83657	1.91
2003	1869	57	212	80762	2.65
2004	1795	25	166	80707	2.46
2005	1598	31	186	72185	2.51

Type I – pallor, perspiration, dizziness, sighing, nausea without vomiting, hyperventilation without other signs or symptoms

Type II – progression of all symptoms of a Type I reaction, bradycardia, shallow respirations, anxiety, vomiting

Type III – progression of all symptoms of a Type II reaction, hyperventilation with neuromuscular excitability, variable color (pale to cyanotic), incontinence, fainting, convulsive movements, true convulsions

Appendix II

These data were obtained from Hemacare, and compare the post donation platelet count with a pre-donation platelet count on the following donation. (see p. 8 comments).

	Pre- and Post-Donation Platelet Study (using ABX instrument)							
	Donation Date	DUN	Sex	Products	Pre-Donation Platelet Count	Post-Donation Platelet Count	Date of Following Donation	Pre-Donation Count on Following Donation
1	12/3/2005	6295588	F	1	240	225	n/a	n/a
2	12/7/2005	6295678	F	1	265	226	12/28/2005	303
3	12/8/2005	6295710	F	1	226	184	n/a	n/a
4	12/7/2005	6295688	F	1	283	206	12/21/2005	365
5	12/4/2005	6295615	F	1	190	137	12/28/2005	159
6	12/1/2005	6295560	F		258	186	12/15/2005	267
7	12/4/2005	6295620	F	1	251	167	12/18/2005	221
8	12/8/2005	6295711	F	1	294	179	n/a	n/a
9	12/4/2005	6295610	F	1	243	142	12/18/2005	236
10	12/7/2005	6295696	F	1	233	129	12/26/2005	207
11	12/7/2005	6295697	F	1	322	178	12/21/2005	317
12	12/4/2005	6295614	F	2	241	210	12/18/2005	234
13	12/7/2005	6295683	F	2	205	164	n/a	n/a
14	11/30/2005	6295536	F	2	249	161	12/28/2005	247
15	11/29/2005	6295526	F	2	295	181	12/13/2005	276
16	12/3/2005	6295595	F	2	289	176	12/19/2005	371
17	12/7/2005	6295695	F	2	303	172	12/21/2005	368
18	11/29/2005	6295519	F	2	249	132	12/13/2005	245
19	11/30/2005	6295541	F	2	273	142	12/14/2005	362
20	12/8/2005	6295707	F	2	347	172	12/14/2005	386
21	11/30/2005	6295547	F	3	374	250	12/14/2005	403
22	11/29/2005	6295528	F	3	466	288	12/13/2005	411
23	12/4/2005	6295623	F	3	354	213	12/18/2005	370
24	12/4/2005	6295612	F	3	438	257	12/18/2005	466
25	12/3/2005	6295590	F	3	368	215	12/17/2005	380
26	12/3/2005	6295592	F	3	359	206	12/17/2005	342
27	12/4/2005	6295606	F	3	436	229	12/18/2005	449
28	11/30/2005	6295542	F	3	381	199	12/14/2005	396
29	11/30/2005	6295534	F	3	338	173	12/14/2005	304
30	11/30/2005	6295552	F	3	310	157	12/16/2005	235
31	12/4/2005	6295611	F	3	275	138	12/18/2005	251
32	12/7/2005	6295693	F	3	413	207	12/21/2005	358
33	12/3/2005	6295601	F	3	326	149	12/17/2005	325
34	12/4/2005	6295621	M	1	218	173	12/18/2005	224
35	12/2/2005	6295581	M	1	227	171	12/16/2005	248
36	12/1/2005	6295558	M	1	200	150	12/22/2005	231

37	11/29/2005	6295531	M	1	195	140	n/a	n/a
38	12/4/2005	6295609	M	1	218	146	12/18/2005	219
39	12/8/2005	6295712	M	1	252	168	n/a	n/a
40	11/30/2005	6295539	M	2	244	195	n/a	n/a
41	11/29/2005	6295517	M	2	239	186	12/27/2005	234
42	12/7/2005	6295702	M	2	227	166	12/21/2005	259
43	12/4/2005	6295604	M	2	226	165	12/18/2005	224
44	11/30/2005	6295553	M	2	364	264	12/28/2005	326
45	12/7/2005	6295680	M	2	221	156	n/a	n/a
46	12/4/2005	6295613	M	2	291	205	12/18/2005	283
47	12/4/2005	6295608	M	2	261	180	12/18/2005	277
48	11/29/2005	6295527	M	2	276	187	12/13/2005	298
49	12/7/2005	6295691	M	2	257	172	12/21/2005	238
50	11/29/2005	6295525	M	2	248	165	12/13/2005	365
51	12/3/2005	6295587	M	2	210	139	12/17/2005	248
52	12/3/2005	6295591	M	2	259	169	12/17/2005	306
53	12/8/2005	6295709	M	2	286	186	n/a	n/a
54	12/7/2005	6295686	M	2	227	147	12/21/2005	230
55	12/3/2005	6295589	M	2	227	147	12/17/2005	232
56	12/8/2005	6295704	M	2	232	149	n/a	n/a
57	11/29/2005	6295530	M	2	274	169	12/13/2005	264
58	12/2/2005	6295580	M	2	248	152	12/16/2005	235
59	11/30/2005	6295544	M	2	241	147	12/14/2005	214
60	12/4/2005	6295618	M	2	251	151	12/18/2005	246
61	12/4/2005	6295605	M	2	265	159	12/18/2005	256
62	12/7/2005	6295689	M	2	260	155	12/21/2005	248
63	11/30/2005	6295550	M	2	309	178	12/14/2005	293
64	12/3/2005	6295593	M	2	238	136	12/23/2005	234
65	12/7/2005	6295698	M	2	366	208	12/21/2005	307
66	12/1/2005	6295556	M	2	251	142	12/19/2005	241
67	12/7/2005	6295701	M	2	291	163	12/21/2005	296
68	12/3/2005	6295586	M	2	289	152	12/17/2005	260
69	12/3/2005	6295599	M	2	259	122	12/17/2005	246
70	11/29/2005	6295521	M	2	357	144	12/13/2005	263
71	11/29/2005	6295523	M	3	317	234	12/13/2005	312
72	12/7/2005	6295690	M	3	283	197	12/21/2005	281
73	12/7/2005	6295687	M	3	262	181	12/21/2005	254
74	12/3/2005	6295597	M	3	303	208	12/17/2005	354
75	11/29/2005	6295522	M	3	320	207	12/19/2005	349
76	12/3/2005	6295594	M	3	322	208	12/17/2005	320
77	12/8/2005	6295703	M	3	405	258	12/22/2005	396
78	12/7/2005	6295692	M	3	355	225	n/a	n/a
70	12/3/2005	6295598	M	3	277	173	n/a	n/a
80	12/8/2005	6295708	M	3	274	169	n/a	n/a
81	11/29/2005	6295524	M	3	300	184	12/27/2005	284
82	12/4/2005	6295624	M	3	319	194	12/18/2005	379
83	12/7/2005	6295694	M	3	260	157	12/21/2005	256
84	12/3/2005	6295600	M	3	354	213	12/17/2005	353

85	11/30/2005	6295538	M	3	282	163	12/14/2005	279
86	12/7/2005	6295682	M	3	274	158	12/21/2005	285
87	12/7/2005	6295699	M	3	322	182	n/a	n/a
88	12/4/2005	6295607	M	3	343	192	12/18/2005	353
89	11/30/2005	6295540	M	3	297	165	12/16/2005	297
90	11/30/2005	6295543	M	3	264	146	12/22/2005	247
91	12/1/2005	6295555	M	3	298	162	12/15/2005	356
92	12/2/2005	6295583	M	3	282	152	12/16/2005	301
93	11/29/2005	6295529	M	3	286	154	12/20/2005	288
94	12/1/2005	6295557	M	3	234	126	12/15/2005	270
95	12/2/2005	6295575	M	3	287	154	n/a	n/a
96	11/29/2005	6295516	M	3	269	140	n/a	n/a
97	12/3/2005	6295602	M	3	262	134	12/17/2005	325
98	11/30/2005	6295551	M	3	365	182	12/19/2005	286
99	12/7/2005	6295679	M	3	295	146	12/21/2005	282
100	11/30/2005	6295549	M	3	319	152	12/14/2005	259
101	12/1/2005	6295559	M	3	265	125	n/a	n/a
102	11/30/2005	6295537	M	3	280	131	12/18/2005	268
193	11/29/2005	6295518	M	3	334	154	12/13/2005	308
104	11/29/2005	6295520	M	3	319	144	n/a	n/a
105	11/30/2005	6295545	M	3	329	142	12/21/2005	327